Birth of a New Macromolecular Architecture: Dendrimers as Quantized Building Blocks for Nanoscale Synthetic Organic Chemistry

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Outline

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1. Introduction

During the 20ᵗʰ century, at least six major technological movements emerged and evolved into mature disciplines that have revolutionized scientific thinking, enhanced the prosperity of many countries, and dramatically improved the human condition. They have been referred to as major technological ages and, in approximate chronological order, are recognized as the *chemical, nuclear, plastics, materials, biotechnology, and computer* ages. An apparent driving force behind each technological age has been the quest for "new properties". As proposed by Philip W. Anderson, (Nobel Laureate in Physics, 1977) an attractive list of rewards, consequences, and possibilities accrue for society whenever scientists are successful at "breaking through new boundaries in the hierarchical complexity of matter" and such new properties emerge.[1] Presently, just such an event may be occurring at the interface of two very active scientific frontiers: the nanotechnology revolution[2,3] and the birth of a new class of macromolecular architecture, namely dendritic polymers.[4,5] This review will describe the emergence of the dendritic state relative to the traditional small-organic-molecule and traditional polymer chemistries. An overview of the critical properties and function of dendritic nanostructures, and the synthetic opportunities that are enabling the design and use of these nanostructures as fundamental building blocks in the emerging field of synthetic nanochemistry, will follow.[6]

Historically, the introduction of well-defined, quantized building blocks (e.g., atoms or monomers) into new synthetic strategies has led to major technological revolutions. Such has been the significance of Dalton's atom modules and Staudinger's monomers in the evolution of traditional small-molecule (organic) chemistry, macromolecular chemistry and, now, nanoscale chemistry (Figure 1).[3] In this regard, the role of the synthetic chemist in five of the above technological ages is the familiar incalculable. Implicit in each of these events is the familiar pattern: advancement to a new covalent complexity level yields novel materials with behaviors that cannot be understood by simple extrapolation of the properties of their building blocks. These advancements generally produce entirely new structures (architectures) with properties that follow strange new rules and require unprecedented explanations, concepts, and generalizations. In essence, "new complexity is not only different, but always more than the linear summation of its components".[1] Such is the expectation as the field of synthetic nanochemistry emerges.

2. Covalent Complexity: Traditional Organic and Polymer Syntheses

As a synthetic and physical organic chemist, I reflect on a handful of profound breakthroughs that contributed so dramatically to our present understanding of synthetic, covalent complexity. My list[6,7] includes: the atom hypothesis (Lavoisier, 1789), the molecular hypothesis (Dalton, 1808), organic chemistry (Wöhler, 1828), architectural isomerism (Berzelius, 1832), and the macromolecular hypothesis (Staudinger, 1926).[8,9]

In 1808, Dalton described his "New System of Chemical Philosophy",[7] a provocative hypothesis for its time, that has since led to the synthesis of literally millions of small inorganic and organic structures of incalculable value. Based on his envisioned atom modules (bricks) and their propensity to form bonds (electronic mortar), an unlimited number of mathematically defined small-molecule compositions, architectures, and chemical functionalities have been combinatorially assembled at the picoscale or subnanoscale level.[10,11] These structures bear no similarity to the structures of their building blocks, exhibit profoundly different properties, and adhere to substantially different bonding rules. The well-known importance of architecture in the determination of properties, even within the same covalent complexity level, was amply demonstrated by Berzelius over 170 years ago with the simple rearrangement of identical elemental compositions into new architectural isomers, allotropes, etc.[10] Most noteworthy was the simple Wöhler isomerization of ammonium cyanate into urea, that ushered in the traditional era of organic chemistry in 1829.[9] The complexity of organic synthesis since that time has been steadily enhanced by utilizing the known hybridization states of carbon and specific heteroatoms to produce key molecular-level hydrocarbon building blocks (modules) and functional groups (connectors). These two construction parameters have been used to assemble literally millions of more complex structures. Relatively small (i.e., < 1
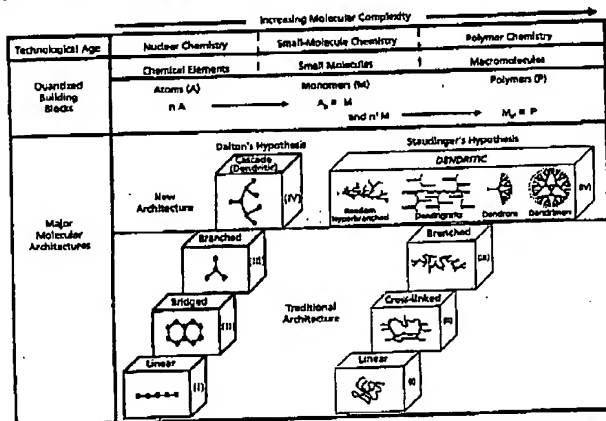

Figure 1. A Comparison of Complexity as a Function of Molecular Architecture, Strategy, Quantized Building Block, and Technological Age. (See Reference 3.)

nm) molecules were produced, the structures of which could be controlled as a function of their shape, mass, flexibility, and functional group placement. Based on the various hybridization states of carbon, at least four major carboskeletal architectures are known.[12,13] They are recognized as the (I) linear, (II) bridged (2D/3D), (III) branched and, more recently, the (IV) dendritic (cascade)[14] type. Consistent with the skeletal isomer principles demonstrated by Berzelius,[15] these major architectural classes exhibit very important differentiated physicochemical properties that are recognized as defining major areas within traditional organic chemistry (e.g., aromatic vs. linear, branched hydrocarbons, etc.). Such analogous macromolecular architectural classes have been recently defined together with their differentiated properties (Figure 2).[15]

In 1926, Herman Staudinger[a] broke a second important complexity barrier—encountered by all synthetic organic chemists at the time—when he demonstrated his macromolecular hypothesis. This profound complexity breakthrough allowed the catenation (polymerization) of small, quantized monomer building blocks into megasized covalent structures (polymers) of nanoscale proportions, albeit with broad, statistical molecular-weight distributions. Three major macromolecular architectures have evolved from Staudinger's hypothesis. The first two architectural classes (i.e., linear and cross-linked)[15] literally defined the origins of traditional polymer science as well as major polymer property differences (i.e., thermoplastics vs. thermosets).[15] The third architectural class (i.e., branched)[16] is presently experiencing dramatic growth related to new polyolefin topologies derived from single-site, metallocene-type catalysts.[17] Historically, it has been widely recognized that macromolecular topologies significantly influence polymer behavior. The advent of each new architecture has invariably produced unique and important properties that have spawned many new products and industries, which have led to essentially all the significant benefits that have emerged from the plastics revolution.[7,18]

3. The Convergence of Nanotechnology and a New Macromolecular Architecture

3.1. The Quest for Quantized Nanoscale Building Blocks

Presently, an international focus is emerging on nanotechnology, which has been described as the "ultimate scientific frontier" that will both define and lead the world into the next industrial revolution.[13,19] While this description is surely exaggerated as today's challenges become tomorrow's routine accomplishments, nanotechnology still faces a very significant obstacle. In essence the growth and development of synthetic nanotechnology will be largely dependent upon successfully identifying appropriate quantized building blocks, much as was required for the development of the traditional fields of chemistry and polymer science. The challenge is to develop critical structure-controlled methodologies to produce appropriate nanoscale modules that will allow cost-effective synthesis and controlled assembly of more complex nanostructures in a very routine manner. Such structures will be macromolecular, require the controlled assembly of as many as 10^3–10^9 atoms, and possess molecular weights ranging from 10^6–10^{10} Daltons.

3.2. The Importance of Controlled Organic Nanostructures in Biology

All critical biological structures (e.g., cells) required for life have been based on the evolutionary development of quantized building blocks derived from controlled organic nanostructures.

This evolutionary development occurred in two significant phases and involved bottom-up synthesis.[3,19,20] Clearly, critical parameters such as mass and dimensions had to increase in size to define the appropriate building modules. The first phase was abiotic and involved molecular evolution from atoms to small molecules. Nature dealt with this problem several billion years ago and shattered this nanoscale synthesis barrier with its evolutionary biological strategy for producing precise nanoscale modules such as DNA, RNA, and proteins. These modules were generally collections of precisely bonded atoms that occupied space with dimensions ranging from 1 to 10^3 nm. These building blocks set the stage for the synthesis of more complex nanostructures, and defined the dimensional (size) scaling that determines essentially all significant molecular-level factors required for initiating and sustaining life. These critical factors include: nanoscale sizes, nanosurfaces and interfaces, nanocontainment, nanoscale transduction and amplification, and information storage.[20] They have important implications, not only in biology, but also in significant abiotic areas such as catalysis, computer miniaturization, nanotribology, sensors, and new materials. Bottom-up synthetic strategies that produce size-monodispersed, well-defined, organic and inorganic nanostructures with dimensions between 1 and 100 nm will be of utmost importance. It will be essential that these strategies allow the systematic construction of nanoscale structures and devices with precise atom-by-atom control as a function of size, shape, and surface chemistry (Figure 3).[19]

3.3. The Wet and Dry Worlds of Nanotechnology

The world of nanotechnology can be divided into two major areas: the wet and dry sides.[18,21] The former, of course, includes the biological domain, wherein the water-based chemistry of living entities is dependent upon hydrophilic nanostructures and devices that may function within biological cells. Dendritic nanopolymers, especially dendrimers, fulfill many applications in the wet world of nanotechnology. In contrast, the dry side includes those applications that derive from hydrophobic architectures. Progress in this second area is expected to enhance the tensile strength of materials, increase their electrical conductivity, or allow the reduction of computer chip size to levels unattainable with traditional bulk materials.

Although substantial progress has been made in the use of fullerenes and carbon nanotubes as nanomodules for dry nanotech
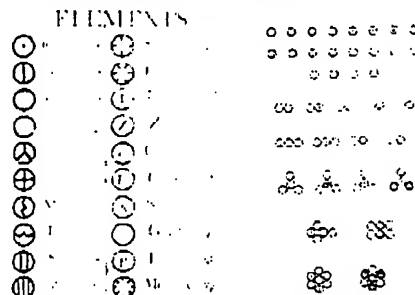

Figure 2. Dalton's Quantized Elemental Building Blocks and Their Combinatorial Possibilities That Led to His *New System of Chemical Philosophy* in 1808. (Reproduced from Reference 13 with Permission from VCH Publishers.)

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applications, their use in biological applications has been hindered by the fact that they are highly hydrophobic and available in only specific sizes (i.e., usually approximately 1 nm).[22] However, recent advances have shown that a limited functionalization of fullerenes may be possible, and that these materials have a promising future in selected biological applications.[23]

4. The Dendritic State

4.1. Dendritic Polymers: A Fourth, Major New Class of Macromolecular Architecture

Dendritic architecture is one of the most pervasive topologies observed in nature at the macro- and microdimensional-length scales (i.e., m to μm). At the nanoscale (molecular level), there are relatively few natural examples of this architecture. Most notable are glycogen and amylopectin, macromolecular hyperbranched structures that nature uses for energy storage. In the polymer field, dendritic topology has now been recognized as a fourth major class of macromolecular architecture.[1,24,25] The signature for such a distinction is the unique repertoire of new properties manifested by this class of polymers.[3,24,26-29] Numerous synthetic strategies have been reported for the preparation of these materials, which have led to a broad range of dendritic structures. Presently, this architectural class consists of four dendritic (cascade) subclasses: (IVa) random hyperbranched polymers, (IVb) dendrigraft polymers, (IVc) dendrons, and (IVd) dendrimers (Figure 4). The order of this subset, from (a) to (d), reflects the relative degree of structural control present in each of these dendritic architectures.[1,3]

All dendritic polymers are open, covalent assemblies of branch cells (Figure 4a). They may be organized as very symmetrical, monodispersed arrays, as is the case for dendrimers, or as irregular, polydispersed assemblies that typically define random, hyperbranched polymers. The respective subclasses and the level of structure control are defined by the propagation methodology used to produce these assemblies, as well as by the branch-cell

(BC) construction parameters. The BC parameters are determined by the composition of the BC monomers, as well as the nature of the excluded volume defined by the BC. The excluded volume of the BC is determined by the length of the arms, the symmetry, rigidity or flexibility, as well as the branching and rotation angles within each of the branch-cell domains. As shown in Figure 4a, these dendritic arrays of branch cells usually manifest covalent connectivity relative to some molecular reference marker (I) or core. As such, these branch-cell arrays may be very nonideal and polydispersed (e.g., $M_w/M_n \cong$ 2-10), as observed for random hyperbranched polymers (IVa), or very ideally organized into highly controlled core-shell-type structures, as noted for dendrons and dendrimers (IVc) and (IVd): $M_w/M_n \cong 1.0000-1.05$ and less. Dendrigraft polymers (IVb) reside between these two extremes of structure control, frequently manifesting narrow polydispersities of $M_w/M_n \cong$ 1.1-1.5, depending on their mode of preparation (Figure 4b).

4.2. Random Hyperbranched Polymers

Flory first hypothesized dendritic polymer concepts,[1,21] which are now recognized to apply to statistical, or random hyperbranched polymers. However, the first experimental confirmation of dendritic topologies did not produce random hyperbranched polymers but rather the more precise, structure-controlled, dendrimer architecture.[1,3] This work was initiated nearly a decade before the first examples of random hyperbranched polymers were confirmed independently by Gunatillake[?] et al. and by Kim and Webster[33,34] in 1988. At that time, Kim and Webster coined the popular term "hyperbranched polymers" that has been widely used to describe this subclass of dendritic macromolecules.

Hyperbranched polymers are typically prepared by polymerization of ABx monomers. When x is 2 or more, polymerization of such monomers gives highly branched
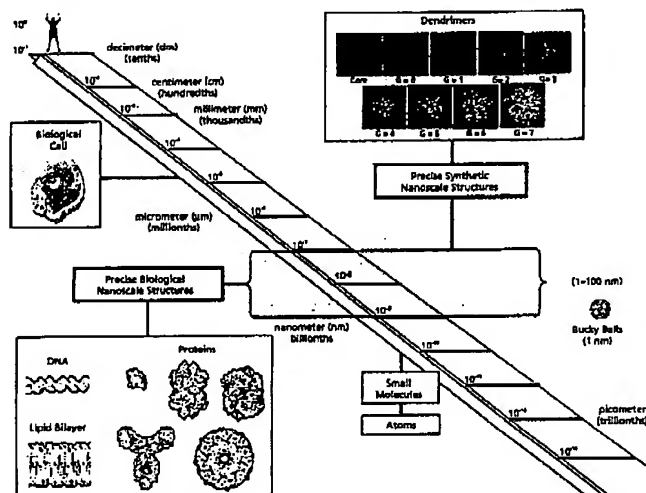

Figure 3. Nanoscale Dimensional Comparison of Poly(amidoamine) Dendrimers [NH, Core] (Gen = 0-7) with a Biological Cell, Proteins, DNA, Lipid Bilayer, Bucky Balls, Small Molecules, and Atoms. (Reproduced from Reference 19 with Permission from CRC Press.)

polymers (see Figure 4), as long as A reacts only with B from another molecule. Reactions between A and B from the same molecule result in termination of polymerization by cyclization. This approach produces hyperbranched polymers with a degree of polymerization n, possessing one unreacted A functional group and $[(x - 1)_n + 1]$ unreacted B terminal groups. In a similar fashion, copolymerization of A_2 and B_3, or other such polyvalent monomers can give hyperbranched polymers.[33,34] If the polymerization is maintained below the gel point by manipulating monomer stoichiometry or limiting polymer conversion.

Random hyperbranched polymers are generally produced by the one-pot polymerization of AB_x-type monomers or macromonomers involving polycondensation, ring opening, or polyaddition reactions. Hence, the products usually have broad, statistical molecular-weight distributions, much as is observed for traditional polymers.

Over the past decade, literally dozens of new AB_2-type monomers have been reported leading to an enormously diverse array of hyperbranched structures. Some general types include poly(phenylene) obtained by the Suzuki coupling;[33,34] poly(phenylacetylenes) prepared by the Heck reaction;[37] polycarbosilanes, polycarbosiloxanes,[38] and poly(siloxysilanes) by hydrosilylation;[39] poly(ether ketones) by nucleophilic aromatic substitution;[40] and polyesters[41] or polyethers[42] by polycondensations or by ring-opening polymerization.[43]

New advances beyond the traditional AB_2 Flory-type, branch-cell monomers have been reported by Fréchet and co-workers.[44,45] They have introduced the concept of latent AB_2 monomers, referred to as self-condensing vinyl polymerizations (SCVP). These monomers, which possess both initiation and propagation properties, may follow two modes of polymerization; namely, polymerization of the double bond (i.e., chain growth) and condensation of the initiating group with the double bond (i.e., step growth). Recent progress involving the derivative process of self-condensing, ring-opening polymerizations (SCROP) has been reviewed by Sunder et al.[46] In addition, the use of enhanced processing techniques, such as pseudo chain growth by slow monomer addition,[47] allow somewhat better control of hyperbranched structures.[48]

4.3. Dendrigraft Polymers

Dendrigraft polymers are the most recently discovered and currently the least understood subset of dendritic polymers. The first examples were reported in 1991 independently by Tomalia et al.[49] and Gauthier and Möller.[49] Whereas traditional monomers are generally employed in constructing dendrimers, reactive oligomers or polymers are used in protect–deprotect or activation schemes to produce dendrigrafts. Consequently, dendrigraft polymers are generally larger structures than dendrimers, grow much faster, and amplify surface groups more dramatically as a function of generational development.

Both hydrophilic (e.g., polyoxazolines and poly-(ethyleneimines)) and hydrophobic dendrigrafts (e.g., polystyrenes) were reported in these early works. These first methodologies involved the iterative grafting of oligomeric reagents derived from living polymerization processes in various iterative *graft-on-graft* strategies. By analogy to dendrimers, each iterative grafting step is referred to as a generation. An important feature of this approach is that branch densities, as well as the size of the grafted branches can be varied independently for each generation. Furthermore, by initiating these iterative grafting steps from a point-like core versus a linear core it is possible to produce spheroidal and cylindrical dendrigrafts, respectively. Depending on the graft densities and molecular weights of the grafted branches, ultrahigh-molecular-weight dendrigrafts (e.g., $M_w > 10^6$ kDa) can be obtained at very low generation levels (e.g., G = 3). Dramatic molecular-weight enhancements vis-à-vis other dendrimer propagation methodologies are possible using dendrigraft techniques.[50] Further elaboration of these dendrigraft principles allowed the synthesis of a variety of core–shell-type dendrigrafts, in which elemental composition as well as the hydrophobic or hydrophilic character of the core were controlled independently.[51]

In general, the above methodologies have involved convergent-type grafting principles, wherein preformed, reactive oligomers are grafted onto successive branched precursors to produce semicontrolled structures. Compared to dendrimers, dendrigraft structures are less controlled since grafting may occur along the entire length of each generational branch, and the exact branching densities are somewhat arbitrary and difficult to control.

More recently, both Gnanou[32,52] and Hedrick[34,53] have developed approaches to dendrigrafts that mimic dendrimer topologies by confining the graft sites to the branch termini for each generation. These methods involve so-called *graft from* techniques, and allow better control of branching topologies and densities as a function
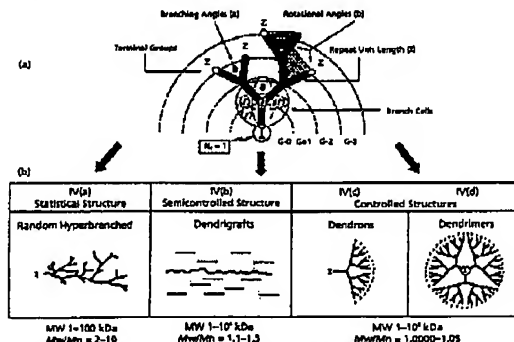

Figure 4. (a) Dendritic Polymers as Open, Covalent Assemblies of Branch Cells. (b) Dendritic Polymers: Subclasses of the Fourth Major New Class of Macromolecular Architecture.